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(54) Title: COMBINATION THERAPY COMPRISING ZD6474 AND A TAXANE

(57) Abstract: The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, particularly a method for the treatment of a cancer involving a solid tumour, which comprises the administration of ZD6474 in combination with a taxane; to a pharmaceutical composition comprising ZD6474 and a taxane; to a combination product comprising ZD6474 and a taxane for use in a method of treatment of a human or animal body by therapy; to a kit comprising ZD6474 and a taxane; to the use of ZD6474 and a taxane in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.

COMBINATION THERAPY COMPRISING ZD6474 AND A TAXANE.

The present invention relates to a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, particularly a method for the treatment of a cancer involving a solid tumour, which comprises the administration of ZD6474 in combination with a taxane; to a pharmaceutical composition comprising ZD6474 and a taxane; to a combination product comprising ZD6474 and a taxane for use in a method of treatment of a human or animal body by therapy; to a kit comprising ZD6474 and a taxane; to the use of ZD6474 and a taxane in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is optionally being treated with ionising radiation.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with *in vitro* endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844).

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a

segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt-1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another fms-like tyrosine kinase receptor, Flt-4. Two of these related RTKs, Flt-1 and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

Quinazoline derivatives which are inhibitors of VEGF receptor tyrosine kinase are described in International Patent Applications Publication Nos. WO 98/13354 and WO 01/32651. In WO 98/13354 and WO 01/32651 compounds are described which possess activity against VEGF receptor tyrosine kinase whilst possessing some activity against EGF receptor tyrosine kinase.

The compound of the present invention, ZD6474, falls within the broad general disclosure of WO 98/13354 and is exemplified in WO 01/32651.

In WO 98/13354 and WO 01/32651 it is stated that compounds of their inventions: "may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment."

WO 98/13354 and WO 01/32651 then go on to describe examples of such conjoint treatment including surgery, radiotherapy and various types of chemotherapeutic agent.

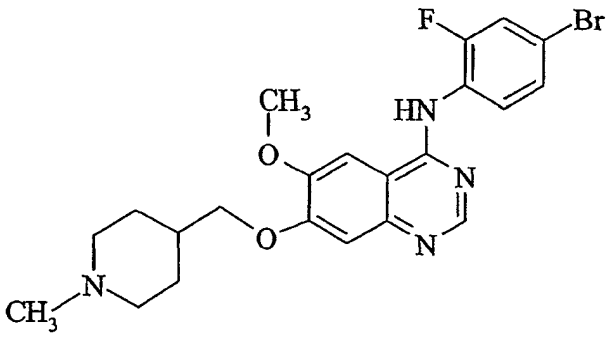
Nowhere in WO 98/13354 and WO 01/32651 does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects.

Unexpectedly and surprisingly we have now found that the particular compound ZD6474 used in combination with a particular selection from the combination therapies listed in WO 98/13354 and WO 01/32651, namely with a taxane, produces significantly better effects than any one of ZD6474 and a taxane used alone. In particular, ZD6474 used in

combination with a taxane produces significantly better effects on solid tumours than any one of ZD6474 and a taxane used alone.

Anti-cancer effects of a method of treatment of the present invention include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present invention include but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. It is expected that when a method of treatment of the present invention is administered to a warm-blooded animal such as a human, in need of treatment for cancer involving a solid tumour, said method of treatment will produce an effect, as measured by, for example, one or more of: the extent of the anti-tumour effect, the response rate, the time to disease progression and the survival rate.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of, 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline, also known as ZD6474:



ZD6474

or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane; wherein ZD6474 and a taxane may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane; wherein ZD6474 and a taxane may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane; wherein ZD6474 and a taxane may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises ZD6474 or a pharmaceutically acceptable salt thereof, and a taxane in association with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a combination product comprising ZD6474 or a pharmaceutically acceptable salt thereof and a taxane, for use in a method of treatment of a human or animal body by therapy.

According to a further aspect of the present invention there is provided a kit comprising ZD6474 or a pharmaceutically acceptable salt thereof, and a taxane.

According to a further aspect of the present invention there is provided a kit comprising:

a) ZD6474 or a pharmaceutically acceptable salt thereof in a first unit dosage form;

b) a taxane in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) ZD6474 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient or carrier, in a first unit dosage form;

b) a taxane together with a pharmaceutically acceptable excipient or carrier, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the simultaneous, sequential or separate administration of an effective amount of a taxane; wherein a taxane may optionally be administered together with a pharmaceutically acceptable excipient or carrier;

to a warm-blooded animal such as a human in need of such therapeutic treatment.

Such therapeutic treatment includes an antiangiogenic and/or vascular permeability effect, an anti-cancer effect and an anti-tumour effect.

A combination treatment of the present invention as defined herein may be achieved by way of the simultaneous, sequential or separate administration of the individual

components of said treatment. A combination treatment as defined herein may be applied as a sole therapy or may involve surgery or radiotherapy or an additional chemotherapeutic agent in addition to a combination treatment of the invention.

Surgery may comprise the step of partial or complete tumour resection, prior to, during or after the administration of the combination treatment with ZD6474 described herein.

Other chemotherapeutic agents for optional use with a combination treatment of the present invention include those described in WO 01/32651 which is incorporated herein by reference. Such chemotherapy may cover five main categories of therapeutic agent:

(i) other antiangiogenic agents including vascular targeting agents;

(ii) cytostatic agents;

(iii) biological response modifiers (for example interferon);

(iv) antibodies (for example edrecolomab); and

(v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology.

The administration of a triple combination of ZD6474, a taxane and ionising radiation may produce effects, such as anti-tumour effects, greater than those achieved with any of ZD6474, a taxane and ionising radiation used alone, greater than those achieved with the combination of ZD6474 and a taxane, greater than those achieved with the combination of ZD6474 and ionising radiation, greater than those achieved with the combination of a taxane and ionising radiation.

According to the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human,

which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane and before, after or simultaneously with an effective amount of ionising radiation.

According to a further aspect of the present invention there is provided a method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane and before, after or simultaneously with an effective amount of ionising radiation, wherein ZD6474 and a taxane may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane and before, after or simultaneously with an effective amount of ionising radiation, wherein ZD6474 and a taxane may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a method for the treatment of a cancer involving a solid tumour in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane and before, after or simultaneously with an effective amount of ionising radiation, wherein ZD6474 and a taxane may each optionally be administered together with a pharmaceutically acceptable excipient or carrier.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a

medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided the use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a medicament for use in the production of an anti-tumour effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

According to a further aspect of the present invention there is provided a therapeutic combination treatment comprising the administration of an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient or carrier, and the administration of an effective amount of a taxane, optionally together with a pharmaceutically acceptable excipient or carrier and the administration of an effective amount of ionising radiation, to a warm-blooded animal such as a human in need of such therapeutic treatment wherein the ZD6474, taxane and ionising radiation may be administered simultaneously, sequentially or separately and in any order.

A warm-blooded animal such as a human which is being treated with ionising radiation means a warm-blooded animal such as a human which is treated with ionising radiation before, after or at the same time as the administration of a medicament or combination treatment comprising ZD6474 and a taxane. For example said ionising radiation may be given to said warm-blooded animal such as a human within the period of a week before to a week after the administration of a medicament or combination treatment comprising ZD6474 and a taxane. This means that ZD6474, a taxane and ionising radiation may be administered separately or sequentially in any order, or may be administered simultaneously. The warm-blooded animal may experience the effect of each of ZD6474, a taxane and radiation simultaneously.

According to one aspect of the present invention the ionising radiation is administered before one of ZD6474 and a taxane or after one of ZD6474 and a taxane.

According to one aspect of the present invention the ionising radiation is administered before both ZD6474 and a taxane or after both ZD6474 and a taxane.

According to one aspect of the present invention ZD6474 is administered to a warm-blooded animal after the animal has been treated with ionising radiation.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be at least equivalent to the addition of the

effects of each of the components of said treatment used alone, that is, of each of ZD6474 and a taxane used alone or of each of ZD6474, a taxane and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be greater than the addition of the effects of each of the components of said treatment used alone, that is, of each of ZD6474 and a taxane used alone or of each of ZD6474, a taxane and ionising radiation used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be a synergistic effect.

According to the present invention a combination treatment is defined as affording a synergistic effect if the effect is therapeutically superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with ZD6474 or a taxane or ionising radiation alone. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to ZD6474 or a taxane or ionising radiation alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect if one of the components is dosed at its conventional dose and the other component(s) is/are dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of ZD6474 or a taxane or ionising radiation may be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

As stated above the combination treatments of the present invention as defined herein are of interest for their antiangiogenic and/or vascular permeability effects. Angiogenesis and/or an increase in vascular permeability is present in a wide range of disease states including cancer (including leukaemia, multiple myeloma and lymphoma), diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, lymphoedema,

endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Combination treatments of the present invention are expected to be particularly useful in the prophylaxis and treatment of diseases such as cancer and Kaposi's sarcoma. In particular such combination treatments of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. In one aspect of the present invention such combination treatments of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of the breast. In one aspect of the present invention such combination treatments of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of the lung, for example in non-small cell lung cancer (NSCLC).

In another aspect of the present invention ZD6474 and a taxane, optionally with ionising radiation, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with EGF especially those tumours which are significantly dependent on EGF for their growth and spread.

In another aspect of the present invention ZD6474 and a taxane, optionally with ionising radiation, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with both VEGF and EGF especially those tumours which are significantly dependent on VEGF and EGF for their growth and spread.

The compositions described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for nasal administration or administration by inhalation, for example as a powder or solution, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream, for rectal administration for example as a suppository or the route of administration may be by direct injection into the tumour or by regional delivery or by local delivery. In other embodiments of the present invention the ZD6474 of the combination treatment may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, intraperitoneally or intratumourally. In general the compositions described herein may be prepared in a conventional manner using conventional excipients. The compositions of the present invention are advantageously presented in unit dosage form.

ZD6474 will normally be administered to a warm-blooded animal at a unit dose within the range 10-500mg per square metre body area of the animal, for example approximately 0.3-15mg/kg in a human. A unit dose in the range, for example, 0.3-15mg/kg,

preferably 0.5-5mg/kg is envisaged and this is normally a therapeutically-effective dose. A unit dosage form such as a tablet or capsule will usually contain, for example 25-500mg of active ingredient. Preferably a daily dose in the range of 0.5-5mg/kg is employed.

Taxanes include paclitaxel and docetaxel. Paclitaxel and docetaxel are commerically available.

In one embodiment of the present invention a taxane is docetaxel.

In one embodiment of the present invention a taxane is paclitaxel.

A taxane may be dosed according to known routes of administration and dosages.

For example paclitaxel may be administered as an infusion over a period of about 24 hours at a dose of 135-200mg/m^2 every 3 weeks. Alternatively for example paclitaxel may be administered as an infusion over a period of about 3 hours at a dose of 135-225mg/m^2 every 3 weeks. Alternatively for example paclitaxel may be administered as an infusion over a period of about 1 hour at a dose of 80-100mg/m^2 every week for a number of weeks. Alternatively for example paclitaxel may be administered as an infusion over a period of about 1 hour at a dose of 200mg/m^2 every 3 weeks. Alternatively for example paclitaxel may be administered as an infusion over a period of about 96 hours at a dose of 120-140mg/m^2 every 3 weeks.

Docetaxel may be dosed in according with known routes of administration and dosages. For example docetaxel may be administered as an infusion over a period of 1 hour at a dose of 55-100mg/m^2 every 3 weeks.

Radiotherapy may be administered according to the known practices in clinical radiotherapy. The dosages of ionising radiation will be those known for use in clinical radiotherapy. The radiation therapy used will include for example the use of γ-rays, X-rays, and/or the directed delivery of radiation from radioisotopes. Other forms of DNA damaging factors are also included in the present invention such as microwaves and UV-irradiation. For example X-rays may be dosed in daily doses of 1.8-2.0Gy, 5 days a week for 5-6 weeks. Normally a total fractionated dose will lie in the range 45-60Gy. Single larger doses, for example 5-10Gy may be administered as part of a course of radiotherapy. Single doses may be administered intraoperatively. Hyperfractionated radiotherapy may be used whereby small doses of X-rays are administered regularly over a period of time, for example 0.1Gy per hour over a number of days. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and on the uptake by cells.

As stated above the size of the dose of each therapy which is required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatments in order to reduce toxicity. The dosages and schedules may vary according to the particular disease state and the overall condition of the patient. Dosages and schedules may also vary if, in addition to a combination treatment of the present invention, one or more additional chemotherapeutic agents is/are used. Scheduling can be determined by the practitioner who is treating any particular patient.

The present invention relates to combinations of a taxane with ZD6474 or with a salt of ZD6474.

Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of ZD6474 and its pharmaceutically acceptable salts. Such salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

ZD6474 may be made, for example, according to any of the following processes illustrated by examples (a) –(c) in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus.

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet; NMR spectra were run on a 400MHz machine at 24°C.

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(viii) the following abbreviations have been used:-

DMF N,N-dimethylformamide
DMSO dimethylsulphoxide
THF tetrahydrofuran
TFA trifluoroacetic acid
NMP 1-methyl-2-pyrrolidinone.]

Process (a)

A solution of 37% aqueous formaldehyde (50µl, 0.6mmol) followed by sodium cyanoborohydride (23mg, 0.36mmol) were added to a solution of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (139mg, 0.3mmol), in a mixture of THF/methanol (1.4ml/1.4ml). After stirring for 1 hour at ambient temperature, water was added and the volatiles were removed under vacuum. The residue was triturated with water, filtered, washed with water, and dried under vacuum. The solid was purified by chromatography on neutral alumina eluting with methylene chloride followed by methylene chloride/ethyl acetate (1/1) followed by methylene chloride/ethyl acetate/methanol (50/45/5). The fractions containing the expected product were evaporated under vacuum. The resulting white solid was dissolved in methylene chloride/methanol (3ml/3ml) and 3N hydrogen chloride in ether (0.5ml) was added. The volatiles were removed under vacuum. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride (120mg, 69%).

MS - ESI: 475-477 $[MH]^+$

The NMR spectrum of the protonated form of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride shows the presence of 2 forms A and B in a ratio A:B of approximately 9:1.

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 1.55-1.7 (m, form A 2H) ; 1.85-2.0 (m, form B 4H) ; 2.03 (d, form A 2H) ; 2.08-2.14 (br s, form A 1H) ; 2.31-2.38 (br s, form B 1H) ; 2.79 (s, form A 3H) ; 2.82 (s, form B 3H) ; 3.03 (t, form A 2H) ; 3.21 (br s, form B 2H) ; 3.30 (br s, form B 2H) ; 3.52 (d, form A 2H) ; 4.02 (s, 3H) ; 4.12 (d, form A 2H) ; 4.30 (d, form B 2H) ; 7.41 (s, 1H) ; 7.5-7.65 (m, 2H) ; 7.81 (d, 1H) ; 8.20 (s, 1H) ; 8.88 (s, 1H)

Elemental analysis:	Found	C 46.0	H 5.2	N 9.6
$C_{22}H_{24}N_4O_2BrF$ 0.3H_2O 2.65HCl	Requires	C 45.8	H 4.8	N 9.7%

The starting material was prepared as follows:

A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (8.35g, 27.8mmol), (prepared, for example, as described in WO 97/22596, Example 1), and 4-bromo-2-fluoroaniline (5.65g, 29.7mmol) in 2-propanol (200ml) was heated at reflux for 4 hours. The resulting precipitate was collected by filtration, washed with 2-propanol and then ether and dried under vacuum to give 7-benzyloxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (9.46g, 78%).

^{1}H NMR Spectrum: ($DMSOd_6$; CD_3COOD) 4.0(s, 3H); 5.37(s, 2H); 7.35-7.5(m, 4H); 7.52-7.62(m, 4H); 7.8(d, 1H); 8.14(9s, 1H); 8.79(s, 1H)

MS - ESI: 456 $[MH]^+$

Elemental analysis:	Found	C 54.0	H 3.7	N 8.7
$C_{22}H_{17}N_3O_2BrF$ 0.9HCl	Requires	C 54.2	H 3.7	N 8.6%

A solution of 7-benzyloxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (9.4g, 19.1mmol) in TFA (90ml) was heated at reflux for 50 minutes. The mixture was allowed to cool and was poured on to ice. The resulting precipitate was collected by filtration and dissolved in methanol (70ml). The solution was adjusted to pH9-10 with concentrated aqueous ammonia solution. The mixture was concentrated to half initial volume by evaporation. The resulting precipitate was collected by filtration, washed with water and then ether, and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (5.66g, 82%).

^{1}H NMR Spectrum: ($DMSOd_6$; CD_3COOD) 3.95(s, 3H); 7.09(s, 1H); 7.48(s, 1H); 7.54(t, 1H); 7.64(d, 1H); 7.79(s, 1H); 8.31(s, 1H)

MS - ESI: 366 $[MH]^+$

Elemental analysis:	Found	C 49.5	H 3.1	N 11.3
$C_{15}H_{11}N_3O_2BrF$	Requires	C 49.5	H 3.0	N 11.5%

While maintaining the temperature in the range 0-5°C, a solution of di-*tert*-butyl dicarbonate (41.7g, 0.19mol) in ethyl acetate (75ml) was added in portions to a solution of ethyl 4-piperidinecarboxylate (30g, 0.19mol) in ethyl acetate (150ml) cooled at 5°C. After stirring for 48 hours at ambient temperature, the mixture was poured onto water (300ml). The organic layer was separated, washed successively with water (200ml), 0.1N aqueous hydrochloric acid (200ml), saturated sodium hydrogen carbonate (200ml) and brine (200ml), dried ($MgSO_4$) and evaporated to give ethyl 4-(1-(*tert*-butoxycarbonyl)piperidine)carboxylate (48g, 98%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.25(t, 3H); 1.45(s, 9H); 1.55-1.70(m, 2H); 1.8-2.0(d, 2H); 2.35-2.5(m, 1H); 2.7-2.95(t, 2H); 3.9-4.1(br s, 2H); 4.15 (q, 2H)

A solution of 1M lithium aluminium hydride in THF (133ml, 0.133mol) was added in portions to a solution of ethyl 4-(1-(*tert*-butoxycarbonyl)piperidine)carboxylate (48g, 0.19mol) in dry THF (180ml) cooled at 0°C. After stirring at 0°C for 2 hours, water (30ml) was added followed by 2N sodium hydroxide (10ml). The precipitate was removed by filtration through diatomaceous earth and washed with ethyl acetate. The filtrate was washed with water, brine, dried ($MgSO_4$) and evaporated to give 1-(*tert*-butoxycarbonyl)-4-hydroxymethylpiperidine (36.3g, 89%).

MS (EI): 215 [M.]+

^{1}H NMR Spectrum: ($CDCl_3$) 1.05-1.2(m, 2H); 1.35-1.55(m, 10H); 1.6-1.8(m, 2H); 2.6-2.8(t, 2H); 3.4-3.6(t, 2H); 4.0-4.2(br s, 2H)

1,4-Diazabicyclo[2.2.2]octane (42.4g, 0.378mol) was added to a solution of 1-(*tert*-butoxycarbonyl)-4-hydroxymethylpiperidine (52.5g, 0.244mol) in *tert*-butyl methyl ether (525ml). After stirring for 15 minutes at ambient temperature, the mixture was cooled to 5°C and a solution of toluene sulphonyl chloride (62.8g, 0.33mmol) in *tert*-butyl methyl ether (525ml) was added in portions over 2 hours while maintaining the temperature at 0°C. After stirring for 1 hour at ambient temperature, petroleum ether (1l) was added. The precipitate was removed by filtration. The filtrate was evaporated to give a solid. The solid was dissolved in ether and washed successively with 0.5N aqueous hydrochloric acid (2x500ml),

water, saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$) and evaporated to give 1-(*tert*-butoxycarbonyl)-4-(4-methylphenylsulphonyloxymethyl)piperidine (76.7g, 85%).

MS (ESI): 392 $[MNa]^+$

^1H NMR Spectrum: ($CDCl_3$) 1.0-1.2(m, 2H); 1.45(s, 9H); 1.65(d, 2H); 1.75-1.9(m, 2H); 2.45(s, 3H); 2.55-2.75(m, 2H); 3.85(d, 1H); 4.0-4.2(br s, 2H); 7.35(d, 2H); 7.8(d, 2H)

Potassium carbonate (414mg, 3mmol) was added to a suspension of 4-(4-bromo-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (546mg, 1.5mmol) in DMF (5ml). After stirring for 10 minutes at ambient temperature, 1-(*tert*-butoxycarbonyl)-4-(4-methylphenylsulphonyloxymethyl)piperidine (636mg, 1.72mmol) was added and the mixture was heated at 95°C for 2 hours. After cooling, the mixture was poured onto cooled water (20ml). The precipitate was collected by filtration, washed with water, and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-7-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-6-methoxyquinazoline (665mg, 79%).

MS - ESI: 561-563 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.15-1.3 (m, 2H), 1.46 (s, 9H), 1.8 (d, 2H), 2.0-2.1 (m, 1H), 2.65-2.9 (m, 2H), 3.95 (s, 3H), 4.02 (br s, 2H), 4.05 (d, 2H), 7.2 (s, 1H), 7.48 (d, 1H), 7.55 (t, 1H), 7.65 (d, 1H), 7.8 (s, 1H), 8.35 (s, 1H), 9.55 (br s, 1H)

TFA (3ml) was added to a suspension of 4-(4-bromo-2-fluoroanilino)-7-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-6-methoxyquinazoline (673mg, 1.2mmol) in methylene chloride (10ml). After stirring for 1 hour at ambient temperature, the volatiles were removed under vacuum. The residue was triturated with a mixture of water/ether. The organic layer was separated. The aqueous layer was washed again with ether. The aqueous layer was adjusted to pH10 with 2N aqueous sodium hydroxide. The aqueous layer was extracted with methylene chloride. The organic layer was dried ($MgSO_4$) and the solvent was removed under vacuum. The solid was triturated with a mixture ether/petroleum ether (1/1), filtered, washed with ether and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (390mg, 70.5%).

MS - ESI: 461-463 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.13-1.3 (m, 2H), 1.75 (d, 2H), 1.87-2.0 (m, 1H), 2.5 (d, 2H), 3.0 (d, 2H), 3.96 (s, 3H), 3.98 (d, 2H), 7.2 (s, 1H), 7.5 (dd, 1H), 7.55 (t, 1H), 7.68 (dd, 1H), 7.80 (s, 1H), 8.36 (s, 1H), 9.55 (br s, 1H)

Elemental analysis:	Found	C 54.5 H 4.9 N 12.1
$C_{21}H_{22}N_4O_2BrF$	Requires	C 54.7 H 4.8 N 12.1%

Process (b)

37% Aqueous formaldehyde (3.5ml, 42mmol) was added to a solution of 4-(4-bromo-2-fluoroanilino)-7-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-6-methoxyquinazoline (3.49g, 6.22mmol), (prepared as described for the starting material in process (a) above), in formic acid (35ml). After heating at 95°C for 4 hours the volatiles were removed under vacuum. The residue was suspended in water and the mixture was adjusted to pH10.5 by slow addition of a solution of 2N sodium hydroxide. The suspension was extracted with ethyl acetate. The organic layer was washed with brine, dried $MgSO_4$ and evaporated to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (2.61g, 88%).

MS - ESI: 475-477 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.3-1.45 (m, 2H), 1.8 (d, 2H), 1.7-1.9 (m, 1H), 1.95 (t, 2H), 2.2 (s, 3H), 2.85 (d, 2H), 3.96 (s, 3H), 4.05 (d, 2H), 7.19 (s, 1H), 7.5 (d, 1H), 7.55 (t, 1H), 7.67 (d, 1H), 7.81 (s, 1H), 8.37 (s, 1H), 9.54 (s, 1H)

Elemental analysis:	Found	C 55.4 H 5.1 N 11.6
$C_{22}H_{24}N_4O_2BrF$	Requires	C 55.6 H 5.1 N 11.8%

Process (c)

A suspension of 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (200mg, 0.62mmol) and 4-bromo-2-fluoroaniline (142mg, 0.74mmol) in isopropanol (3ml) containing 6N hydrogen chloride in isopropanol (110µl, 0.68ml) was heated at reflux for 1.5 hours. After cooling, the precipitate was collected by filtration, washed with isopropanol followed by ether and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride (304mg, 90%).

Elemental analysis:	Found	C 47.9 H 4.9 N 10.0
$C_{22}H_{24}N_4O_2BrF$ 0.5H_2O 1.8HCl	Requires	C 48.2 H 5.0 N 10.1%

0.08 isopropanol

The NMR spectrum of the protonated form of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride shows the presence of two forms A and B in a ratio A:B of approximately 9:1.

^{1}H NMR Spectrum: ($DMSOd_6$) 1.6-1.78 (m, form A 2H); 1.81-1.93 (br s, form B 4H); 1.94-2.07 (d, form A 2H); 2.08-2.23 (br s, form A 1H); 2.29-2.37 (br s, form B 1H); 2.73 (d, form A 3H); 2.77 (d, form B 3H); 2.93-3.10 (q, form A 2H); 3.21 (br s, form B 2H); 3.27 (br s, form B 2H); 3.42-3.48 (d, form A 2H); 4.04 (s, 3H); 4.10 (d, form A 2H); 4.29 (d, form B 2H); 7.49 (s, 1H) ; 7.53-7.61 (m, 2H); 7.78 (d, 1H); 8.47 (s, 1H); 8.81 (s, 1H); 10.48 (br s, form A 1H); 10.79 (br s, form B 1H); 11.90 (br s, 1H)

For another NMR reading, some solid potassium carbonate was added into the DMSO solution of the 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride described above, in order to release the free base in the NMR tube. The NMR spectrum was then recorded again and showed only one form as described below:

^{1}H NMR Spectrum: ($DMSOd_6$; solid potassium carbonate) 1.3-1.45 (m, 2H) ; 1.75 (d, 2H) ; 1.7-1.9(m, 1H) ; 1.89 (t, 2H) ; 2.18 (s, 3H) ; 2.8 (d, 2H) ; 3.98 (s, 3H) ; 4.0 (d, 2H) ; 7.2 (s, 1H) ; 7.48 (d, 1H) ; 7.55 (t, 1H) ; 7.68 (d, 1H) ; 7.8 (s, 1H) ; 8.35 (s, 1H) ; 9.75 (s, 1H)

A sample of 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (free base) was generated from the 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline hydrochloride, (prepared as described above), as follows:

4-(4-Bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxyquinazoline hydrochloride (50mg) was suspended in methylene chloride (2ml) and was washed with saturated sodium hydrogen carbonate. The methylene chloride solution was dried ($MgSO_4$) and the volatiles were removed by evaporation to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (free base). The NMR of the free base so generated shows only one form as described below:

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.45 (m, 2H) ; 1.76 (d, 2H) ; 1.7-1.9(m, 1H) ; 1.9 (t, 2H) ; 2.19 (s, 3H) ; 2.8 (d, 2H) ; 3.95 (s, 3H) ; 4.02 (d, 2H) ; 7.2 (s, 1H) ; 7.48 (d, 1H) ; 7.55 (t, 1H) ; 7.68 (dd, 1H) ; 7.8 (s, 1H) ; 8.38 (s, 1H) ; 9.55(br s, 1H)

For another NMR reading, some CF_3COOD was added into the NMR DMSO solution of the 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (free base) described above and the NMR spectrum was recorded again. The spectrum of the

protonated form of the 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline trifluoroacetate salt so obtained shows the presence of two forms A and B in a ratio A:B of approximately 9:1.

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 1.5-1.7 (m, form A 2H); 1.93 (br s, form B 4H); 2.0-2.1 (d, form A 2H); 2.17 (br s, form A 1H); 2.35 (br s, form B1H); 2.71 (s, form A 3H); 2.73 (s, form B 3H); 2.97-3.09 (t, form A 2H); 3.23 (br s, form B 2H); 3.34 (br s, form B 2H); 3.47-3.57 (d, form A 2H); 4.02 (s, 3H); 4.15 (d, form A 2H); 4.30 (d, form B 2H); 7.2 (s, 1H); 7.3-7.5 (m, 2H); 7.6 (d, 1H); 7.9 (s, 1H); 8.7 (s, 1H)

The starting material was prepared as follows:

1-(*tert*-Butoxycarbonyl)-4-(4-methylphenylsulphonyloxymethyl)piperidine (40g, 0.11mol), (prepared as described for the starting material in process (a) above), was added to a suspension of ethyl 4-hydroxy-3-methoxybenzoate (19.6g, 0.1mol) and potassium carbonate (28g, 0.2mol) in dry DMF (200ml). After stirring at 95°C for 2.5 hours, the mixture was cooled to ambient temperature and partitioned between water and ethyl acetate/ether. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The resulting oil was crystallised from petroleum ether and the suspension was stored overnight at 5°C. The solid was collected by filtration, washed with petroleum ether and dried under vacuum to give ethyl 4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-3-methoxybenzoate (35g, 89%).

m.p. 81-83°C

MS (ESI): 416 $[MNa]^+$

^{1}H NMR Spectrum: ($CDCl_3$) 1.2-1.35(m, 2H); 1.4(t, 3H); 1.48(s, 9H); 1.8-1.9(d, 2H); 2.0-2.15(m, 2H); 2.75(t, 2H); 3.9(d, 2H); 3.95(s, 3H); 4.05-4.25(br s, 2H); 4.35(q, 2H); 6.85(d, 1H); 7.55(s, 1H); 7.65(d, 1H)

Elemental analysis:	Found	C 63.4	H 8.0	N 3.5	
$C_{21}H_{31}NO_6$ $0.3H_2O$	Requires	C 63.2	H 8.0	N 3.5%	

Formaldehyde (12M, 37% in water, 35ml, 420mmol) was added to a solution of ethyl 4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-3-methoxybenzoate (35g, 89mmol) in formic acid (35ml). After stirring at 95°C for 3 hours, the volatiles were removed by evaporation. The residue was dissolved in methylene chloride and 3M hydrogen chloride in ether (40ml, 120mmol) was added. After dilution with ether, the mixture was triturated until a solid was formed. The solid was collected by filtration, washed with ether and dried under

vacuum overnight at 50°C to give ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (30.6g, quant.).

MS (ESI): 308 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.29(t, 3H); 1.5-1.7(m, 2H); 1.95(d, 2H); 2.0-2.15(br s, 1H); 2.72(s, 3H); 2.9-3.1(m, 2H); 3.35-3.5(br s, 2H); 3.85(s, 3H); 3.9-4.05(br s, 2H); 4.3(q, 2H); 7.1(d, 1H); 7.48(s, 1H); 7.6(d, 1H)

A solution of ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (30.6g, 89mmol) in methylene chloride (75ml) was cooled to 0-5°C. TFA (37.5ml) was added followed by the dropwise addition over 15 minutes of a solution of fuming 24N nitric acid (7.42ml, 178mmol) in methylene chloride (15ml). After completion of the addition, the solution was allowed to warm up and stirred at ambient temperature for 2 hours. The volatiles were removed under vacuum and the residue was dissolved in methylene chloride (50ml). The solution was cooled to 0-5°C and ether was added. The precipitate was collected by filtration, and dried under vacuum at 50°C. The solid was dissolved in methylene chloride (500ml) and 3M hydrogen chloride in ether (30ml) was added followed by ether (500ml). The solid was collected by filtration and dried under vacuum at 50°C to give ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)-6-nitrobenzoate (28.4g, 82%).

MS (ESI): 353 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.3(t, 3H); 1.45-1.65(m, 2H); 1.75-2.1(m, 3H); 2.75(s, 3H); 2.9-3.05(m, 2H); 3.4-3.5(d, 2H); 3.95(s, 3H); 4.05(d, 2H); 4.3(q, 2H); 7.32(s, 1H); 7.66(s, 1H)

A suspension of ethyl 3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)-6-nitrobenzoate (3.89g, 10mmol) in methanol (80ml) containing 10% platinum on activated carbon (50% wet) (389mg) was hydrogenated at 1.8 atmospheres pressure until uptake of hydrogen ceased. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in water (30ml) and adjusted to pH10 with a saturated solution of sodium hydrogen carbonate. The mixture was diluted with ethyl acetate/ether (1/1) and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate/ether and the organic layers were combined. The organic layers were washed with water, brine, dried ($MgSO_4$), filtered and evaporated. The resulting solid was triturated in a mixture of ether/petroleum ether, filtered, washed with petroleum ether and dried under vacuum at 60°C to give ethyl 6-amino-3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (2.58g, 80%).

m.p. 111-112°C

MS (ESI): 323 $[MH]^+$

^{1}H NMR Spectrum: ($CDCl_3$) 1.35(t, 3H); 1.4-1.5(m, 2H); 1.85(m, 3H); 1.95(t, 2H); 2.29(s, 3H); 2.9(d, 2H); 3.8(s, 3H); 3.85(d, 2H); 4.3(q, 2H); 5.55(br s, 2H); 6.13(s, 1H); 7.33(s, 1H)

Elemental analysis:	Found	C 62.8	H 8.5	N 8.3	
$C_{17}H_{26}N_2O_4$ 0.2H_2O	Requires	C 62.6	H 8.2	N 8.6%	

A solution of ethyl 6-amino-3-methoxy-4-(1-methylpiperidin-4-ylmethoxy)benzoate (16.1g, 50mmol) in 2-methoxyethanol (160ml) containing formamidine acetate (5.2g, 50mmol) was heated at 115°C for 2 hours. Formamidine acetate (10.4g, 100mmol) was added in portions every 30 minutes over 4 hours. Heating was prolonged for 30 minutes after the last addition. After cooling, the volatiles were removed under vacuum. The solid was dissolved in ethanol (100ml) and methylene chloride (50ml). The precipitate was removed by filtration and the filtrate was concentrated to a final volume of 100ml. The suspension was cooled to 5°C and the solid was collected by filtration, washed with cold ethanol followed by ether and dried under vacuum overnight at 60°C to give 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (12.7g, 70%).

MS (ESI): 304 $[MH]^+$

^{1}H NMR Spectrum: ($DMSOd_6$) 1.25-1.4(m, 2H); 1.75(d, 2H); 1.9(t, 1H); 1.9(s, 3H); 2.16(s, 2H); 2.8(d, 2H); 3.9(s, 3H); 4.0(d, 2H); 7.11(s, 1H); 7.44(s, 1H); 7.97(s, 1H)

A solution of 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (2.8g, 9.24mmol) in thionyl chloride (28ml) containing DMF (280µl) was heated at reflux at 85°C for 1 hour. After cooling, the volatiles were removed by evaporation. The precipitate was triturated with ether, filtered, washed with ether and dried under vacuum. The solid was dissolved in methylene chloride and saturated aqueous sodium hydrogen carbonate was added. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated to give 4-chloro-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (2.9g, 98%).

MS (ESI): 322 $[MH]^+$

^{1}H NMR Spectrum: ($DMSOd_6$) 1.3-1.5(m, 2H); 1.75-1.9(m, 3H); 2.0(t, 1H); 2.25(s, 3H); 2.85(d, 2H); 4.02(s, 3H); 4.12(d, 2H); 7.41(s, 1H); 7.46(s, 1H); 8.9(s, 1H)

Alternatively, the 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one can be prepared as follows:

Sodium hydride (1.44g of a 60% suspension in mineral oil, 36mmol) was added in portions over 20 minutes to a solution of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-

one (8.46g, 30mmol), (prepared, for example, as described in WO 97/22596, Example 1), in DMF (70ml) and the mixture was stirred for 1.5 hours. Chloromethyl pivalate (5.65g, 37.5mmol) was added in portions and the mixture stirred for 2 hours at ambient temperature. The mixture was diluted with ethyl acetate (100ml) and poured onto ice/water (400ml) and 2N hydrochloric acid (4ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate, the combined extracts were washed with brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with a mixture of ether and petroleum ether, the solid was collected by filtration and dried under vacuum to give 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (10g, 84%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.11(s, 9H); 3.89(s, 3H); 5.3(s, 2H); 5.9(s, 2H); 7.27(s, 1H); 7.35(m, 1H); 7.47(t, 2H); 7.49(d, 2H); 7.51(s, 1H); 8.34(s, 1H)

A mixture of 7-benzyloxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (7g, 17.7mmol) and 10% palladium-on-charcoal catalyst (700mg) in ethyl acetate (250ml), DMF (50ml), methanol (50ml) and acetic acid (0.7ml) was stirred under hydrogen at atmospheric pressure for 40 minutes. The catalyst was removed by filtration and the solvent removed from the filtrate by evaporation. The residue was triturated with ether, collected by filtration and dried under vacuum to give 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (4.36g, 80%).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.1(s, 9H); 3.89(s, 3H); 5.89(s, 2H); 7.0(s, 1H); 7.48(s, 1H); 8.5(s, 1H)

Triphenylphosphine (1.7g, 6.5mmol) was added under nitrogen to a suspension of 7-hydroxy-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.53g, 5mmol) in methylene chloride (20ml), followed by the addition of 1-(*tert*-butoxycarbonyl)-4-(hydroxymethyl)piperidine (1.29g, 6mmol), (prepared as described for the starting material in process (a) above), and by a solution of diethyl azodicarboxylate (1.13g, 6.5mmol) in methylene chloride (5ml). After stirring for 30 minutes at ambient temperature, the reaction mixture was poured onto a column of silica and was eluted with ethyl acetate/petroleum ether (1/1 followed by 6/5, 6/4 and 7/3). Evaporation of the fractions containing the expected product led to an oil that crystallised following trituration with pentane. The solid was collected by filtration and dried under vacuum to give 7-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (232g, 92%).
MS - ESI: 526 $[MNa]^+$

^{1}H NMR Spectrum: ($CDCl_3$) 1.20 (s, 9H), 1.2-1.35 (m, 2H), 1.43 (s, 9H), 1.87 (d, 2H), 2.05-2.2 (m, 1H), 2.75 (t, 2H), 3.96 (d, 2H), 3.97 (s, 3H), 4.1-4.25 (br s, 2H), 5.95 (s, 2H), 7.07 (s, 1H), 7.63 (s, 1H), 8.17 (s, 1H)

Elemental analysis:	Found	C 61.8	H 7.5	N 8.3	
$C_{26}H_{37}N_3O_7$	Requires	C 62.0	H 7.4	N 8.3%	

A solution of 7-(1-(*tert*-butoxycarbonyl)piperidin-4-ylmethoxy)-6-methoxy-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (2.32g, 4.6mmol) in methylene chloride (23ml) containing TFA (5ml) was stirred at ambient temperature for 1 hour. The volatiles were removed under vacuum. The residue was partitioned between ethyl acetate and sodium hydrogen carbonate. The organic solvent was removed under vacuum and the residue was filtered. The precipitate was washed with water, and dried under vacuum. The solid was azeotroped with toluene and dried under vacuum to give 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.7g, 92%).

MS - ESI: 404 $[MH]^+$

^{1}H NMR Spectrum: ($DMSOd_6$; CF_3COOD) 1.15 (s, 9H), 1.45-1.6 (m, 2H), 1.95 (d, 2H), 2.1-2.25 (m, 1H), 2.95 (t, 2H), 3.35 (d, 2H), 3.95 (s, 3H), 4.1 (d, 2H), 5.95 (s, 2H), 7.23 (s, 1H), 7.54 (s, 1H), 8.45 (s, 1H)

A 37% aqueous solution of formaldehyde (501µl, 6mmol) followed by sodium cyanoborohydride (228mg, 3.6mmol) were added in portions to a solution of 6-methoxy-7-(piperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.21g, 3mmol) in a mixture of THF/methanol (10ml/10ml). After stirring for 30 minutes at ambient temperature, the organic solvents were removed under vacuum and the residue was partitioned between methylene chloride and water. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and the volatiles were removed by evaporation. The residue was triturated with ether and the resulting solid was collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.02g, 82%).

MS - ESI: 418 $[MH]^+$

^{1}H NMR Spectrum: ($CDCl_3$) 1.19 (s, 9H), 1.4-1.55 (m, 2H), 1.9 (d, 2H), 2.0 (t, 2H), 1.85-2.1 (m, 1H), 2.3 (s, 3H), 2.92 (d, 2H), 3.96 (s, 3H), 3.99 (d, 2H), 5.94 (s, 2H), 7.08 (s, 1H), 7.63 (s, 1H), 8.17 (s, 1H)

A saturated solution of ammonia in methanol (14ml) was added to a solution of 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3-((pivaloyloxy)methyl)-3,4-dihydroquinazolin-4-one (1.38g, 3.3mmol) in methanol (5ml). After stirring for 20 hours at ambient temperature, the suspension was diluted with methylene chloride (10ml). The solution was filtered. The filtrate was evaporated under vacuum and the residue was triturated with ether, collected by filtration, washed with ether and dried under vacuum to give 6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)-3,4-dihydroquinazolin-4-one (910mg, 83%).

MS - ESI: 304 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 1.3-1.45 (m, 2H), 1.75 (d, 2H), 1.7-1.85 (m, 1H), 1.9 (t, 2H), 2.2 (s, 3H), 2.8 (d, 2H), 3.9 (s, 3H), 4.0 (d, 2H), 7.13 (s, 1H), 7.45 (s, 1H), 7.99 (s, 1H)

For example, the following tests may be used to demonstrate the activity of ZD6474 in combination with a taxane.

a) GEO human colon cancer xenograft model: ZD6474 dosed intraperitoneally

Female BALB/c athymic (*nu+/nu+*) mice 4-6 weeks of age were injected subcutaneously (s.c.) with GEO human colon cancer cells (10^7cells resuspended in 200µl Matrigel) on day 0. Treatment was initiated on day 7 after s.c. implantation of GEO cells when the average tumour volume was 0.25 (±0.05) cm^3. 10 mice per group were treated either with intraperitoneal (i.p.) paclitaxel (400 µg/mouse) on days 7, 14, 21 and 28, or with ZD6474 (100mg/kg/day i.p. suspended in a 1% (v/v) solution of polyoxyethylene (20) sorbitan mono-oleate in deionised water) on days 7-11, 14-18, 21-25 and 28-32, or with a combination of both agents. In the case of combination treatments, where mice received both agents on the same day, paclitaxel was given 10-15 minutes before ZD6474. Tumour size was measured using the formula $\pi/6$ x larger diameter x (smaller diameter)^2.

Table 1: Antitumour activity of ZD6474 alone or in combination with paclitaxel on GEO human colon cancer xenografts

Treatment	Average tumour volume on day 28 after tumour cell injection (cm^3)	Average time (days) from day 28 to reach an average tumour volume of $2cm^3$ (approximately 10% of mouse body weight)
Control	1.95 (±0.15)	-
Paclitaxel	0.95 (±0.1)	14 (±3)
ZD6474 (100 mg/kg)	0.1 (±0.05)	29 (±2)
Paclitaxel + ZD6474 (100 mg/kg)	0.01 (±0.01)	58 (±4)*

*Two out of the 10 mice in this group were without histological evidence of GEO tumours at sacrifice on day 110. The data on these two mice has not been included in calculating the growth delay in days.

The average tumour volume on day 28 following tumour cell injection in control mice, 1.95 (±0.15) cm^3, was approximately 10% of nude mouse body weight and mice in this group were sacrificed at this time. Mice in each of the treatment groups were sacrificed when their tumours reached a comparable size.

Statistical evaluations of time to reach a tumour volume of $2cm^3$ has been done using the Mantel-Cox logrank test with the following results: ZD6474 (100 mg/kg) versus control (p= 0.001); paclitaxel + ZD6474 (100 mg/kg) versus control (p= 0.0001); paclitaxel + ZD6474 (100 mg/kg) versus paclitaxel (p= 0.001); paclitaxel + ZD6474 (100 mg/kg) versus ZD6474 (100 mg/kg) (p= 0.01).

The results show that the use of ZD6474 in combination with paclitaxel produces a significantly greater effect against the tumour than either ZD6474 or paclitaxel used alone.

(b) SW620 human colon cancer xenograft model: ZD6474 dosed orally

Tumour implantation procedures were performed on mice of at least 8 weeks of age. Human tumour xenografts were grown in female Alderley Park athymic (*nu/nu* genotype, Swiss) mice housed in negative pressure isolators (PFI Systems Ltd., Oxon, UK).

SW620 cells were implanted into athymic mice ($1x10^6$ cells/mouse in 50% matrigel in serum-free media; s.c left flank) and allowed to grow, for example for 5 days, at which point randomisation was carried out (10 or 12 animals/group). Animals were treated with either paclitaxel (for example $5mgml^{-1}$; i.p. twice daily for 3 days) or vehicle (3% cremophor: 3%methanol: 94% PBS/A; i.p. twice daily for 3 days). Animals were then dosed with either ZD6474 suspended in a 1% (v/v) solution of polyoxyethylene (20) sorbitan mono-oleate in deionised water (orally (p.o.)) or the corresponding vehicle once daily at 0.1ml/10g body weight (p.o). Different doses of ZD6474 were used for different treatment groups for example 25mg/kg or 50mg/kg.

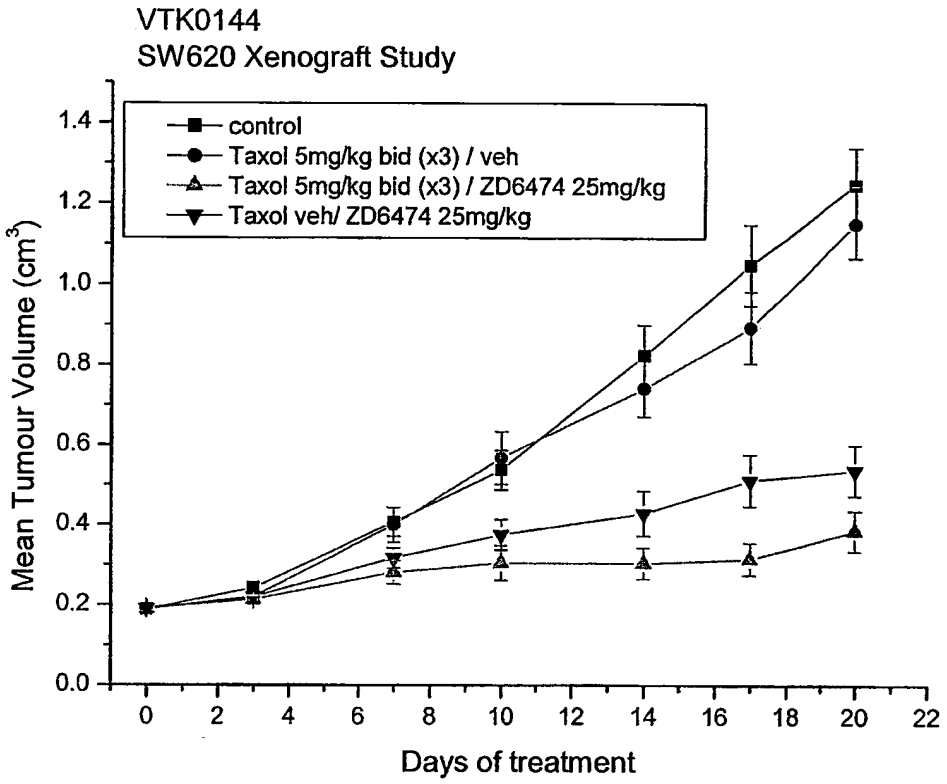
ZD6474 may be given before, after or simultaneously with paclitaxel; the dosage regimens can be varied.

Tumour volumes were assessed at least twice weekly by bilateral Vernier caliper measurement and, taking length to be the longest diameter across the tumour and width the corresponding perpendicular, calculated using the formula ($\pi/6$) x (length x width) x v(length x width). Growth inhibition from the start of treatment was assessed by comparison of the differences in tumour volume between control and treated groups.

Statistical significance was evaluated using a one-tailed two-sample t-test.

The data for a combination study wherein ZD6474 was dosed at 25mg/kg is shown in Figure 1. The mean tumour volume was significantly less in the combination group on days 17 and 20 compared to the group that received ZD6474 alone ($p=0.008$ and $p=0.032$ respectively).

Figure 1


VTK0144
SW620 Xenograft Study
control
Taxol 5mg/kg bid (x3) / veh
Taxol 5mg/kg bid (x3) / ZD6474 25mg/kg
Taxol veh/ ZD6474 25mg/kg
Mean Tumour Volume (cm3)
Days of treatment
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0
2
4
6
8
10
12
14
16
18
20
22

5

Claims

1. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane.

2. A method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane.

3. A method according to claim 2 for the treatment of a cancer involving a solid tumour.

4. A pharmaceutical composition which comprises ZD6474 or a pharmaceutically acceptable salt thereof, and a taxane in association with a pharmaceutically acceptable excipient or carrier.

5. A kit comprising ZD6474 or a pharmaceutically acceptable salt thereof, and a taxane.

6. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human.

7. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human.

8. Use according to claim 7 wherein the anti-cancer effect comprises an anti-tumour effect.

9. A method for the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane and before, after or simultaneously with an effective amount of ionising radiation.

10. A method for the treatment of a cancer in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of ZD6474 or a pharmaceutically acceptable salt thereof, before, after or simultaneously with an effective amount of a taxane and before, after or simultaneously with an effective amount of ionising radiation.

11. A method according to claim 10 for the treatment of a cancer involving a solid tumour.

12. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

13. Use of ZD6474 or a pharmaceutically acceptable salt thereof and a taxane in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as a human which is being treated with ionising radiation.

14. Use according to claim 13 wherein the anti-cancer effect comprises an anti-tumour effect.

INTERNATIONAL SEARCH REPORT

Internatic .pplication No
PCT/GB 02/05021

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/517 A61P35/00 A61K31/337 A61K41/00
//(A61K31/517,31:337)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, MEDLINE, CHEM ABS Data, WPI Data, PAJ, CANCERLIT, SCISEARCH BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 32651 A (HENNEQUIN LAURENT FRANCOIS AND ;THOMAS ANDREW PETER (GB); ASTRAZEN) 10 May 2001 (2001-05-10) cited in the application page 26, line 22 -page 27, line 30 page 28, line 5 - line 17 examples 2A-2C page 26, line 27 - line 31 ---	1-14
X	MOLL J. ET AL: "Antiangiogenic therapy: Preclinical premise and promise." MOLECULAR MEDICINE TODAY, (2000) 6/5 (188-189)., XP001134946 page 188, column 2 -column 3 --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2003	27/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Strack, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internatic pplication No
PCT/GB 02/05021

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FOLKMAN J. ET AL: "Angiogenesis research: Guidelines for translation to clinical application" THROMBOSIS AND HAEMOSTASIS, (2001) 86/1 (23-33)., XP008011920 table 1 page 31, paragraph 1 - paragraph 3 page 26, column 1, paragraph 3 -column 2, paragraph 1 ---	1-8
Y	EISENHAUER E. ET AL: "Impact of new non-cytotoxics in the treatment of ovarian cancer." INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER, (2001) 11/SUPPL. 1 (68-72), XP001062441 page 71; table 3 page 71, column 1, paragraph 2 -column 2, paragraph 1 ---	9-14
Y	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; FABBRO D ET AL: "PKC412 --a protein kinase inhibitor with a broad therapeutic potential." retrieved from STN Database accession no. NLM10888033 XP002227304 abstract & ANTI-CANCER DRUG DESIGN, (2000 FEB) 15 (1) 17-28., ---	9-14
A	WO 98 13354 A (LOHMANN JEAN JACQUES MARCEL ;HENNEQUIN LAURENT FRANCOIS AND (FR);) 2 April 1998 (1998-04-02) cited in the application page 46, line 17 -page 47, line 19 -----	1-8

INTERNATIONAL SEARCH REPORT

Inter ial application No.
PCT/GB 02/05021

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-3 and 9-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-14 relate to a large number of possible compounds ("taxanes"). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, present claims 1, 6, 9 and 12 relate to the treatment of diseases which actually are not well defined. The claims cover all uses relating to the term "production of an antiangiogenic and/or vascular permeability reducing effect" whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a limited number of such uses. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole scope of the claims is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define a use by reference to a mechanistic term which does not allow any practical application in the form of a defined, real treatment of a pathological condition. This lack of clarity in the present case is such as to render a meaningful search over the whole scope of the claims impossible.

Consequently, the search for the first invention has been carried out for those parts of the application which do appear to be clear, supported and disclosed, namely the use of ZD6474 in combination with paclitaxel or docetaxel in relation to the treatment of cancer with due regard to the general idea underlying the present invention.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati[illegible]pplication No
PCT/GB 02/05021

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0132651	A	10-05-2001	AU	1288601 A	14-05-2001
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